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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,747	09/22/1999	MAR TORMO	UTSC:550—/1PAR	4363

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DAVID L PARKER
ARNOLD WHITE & DURKEE
PO BOX 4433
HOUSTON, TX 77210

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,747	TORMO ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 22-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/30/04, 8/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action supercedes the Office Action filed 8/28/2001. The prior communication filed 02/08/2005 is hereby vacated. Claims 1-20 and 22-49 are pending and currently under examination.

Oath/Declaration

The objection to the declaration set forth in the prior Office actions filed 07/10/2000 and 02/01/2001 has been overcome based upon the declarations under 37 CFR 1.132 filed 06/06/2002 and the Petition decision filed on 03/04/2003.

Double Patenting

The rejection of claims 10-20, 25 and 39-49 under the provisional Double Patenting doctrine based on copending Application 08/726,811, as set forth in the Office Action mailed 02/01/2001, has not been overcome and therefore is maintained because the claims are still pending in both applications.

The rejection of claims 1-9 and 21-38 under the obvious type Double Patenting doctrine over U.S. Patent Nos: 5,855,911 and 6,042,846 in view of Evan or Green or Reed and in further view of Tormo et al., in the Office Action mailed 02/01/2001 has been withdrawn.

Claim Rejections - 35 USC § 103

The declaration under 37 CFR 1.132 filed 08/07/2001 is sufficient to overcome the rejection of claims 1-9 and 21-38 based upon 35 U.S.C. 103(a) as being unpatentable over Evan (WO 93/20200) or Reed (WO 95/08350) or Green et al. (U.S. Patent No.5, 583,034) each in view of Tari et al. (U.S. Patent No. 5,417,978) and Tormo et al. (Proceedings of the American Association for Cancer Research, Vol. 37, 1996), in the Office Action mailed 02/01/2001.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 21-24 and 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan (WO 93/20200) or Reed (WO 95/08350) or Green et al. (U.S. Patent No. 5, 583,034) each in view of Lopez-Berestein et al. (U.S. Patent No. 5, 855,911).

Evan teach the use of an antisense molecule target to Bcl-2 to prevent the expression of the Bcl-2 protein (page 7, lines 10-29), wherein the oligonucleotide is preferably targeted to the translation initiation codon of Bcl-2 and comprises SEQ ID NO. 1 (page 18, lines 26-30) and that the expression construct is preferably delivered via a liposome (page 59, lines 6-7).

Reed teach an antisense oligonucleotide which is targeted to bcl-2 and inhibits the expression of bcl-2 protein (page 3, lines 2-22). The antisense oligonucleotide taught by Reed is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO. 1 (page 13, lines 2-5). Reed teaches that the antisense oligonucleotide, or a vector which expressed the antisense oligonucleotide, is preferably delivered via a liposome (page 14, lines 16-25).

Green et al. teach antisense oligonucleotides targeted to anti-apoptotic genes, including bcl-2 (column 3, lines 51-67) wherein said antisense oligonucleotides are preferably targeted to the translation initiation codon of the target gene (column 4, lines 46-51). Green et al. teach that the antisense oligonucleotides can be encapsulated into liposomes for administration (see for example column 6, lines 60-63) may be delivered using an expression vector encoding the antisense oligonucleotide (column 6, lines 8-10).

Evan, Reed or Green et al. do not teach antisense with a p-ethoxy backbone modification and further do not teach a liposome composed of neutral lipids nor teach the liposomes composed of phosphatidycholine, phosphatidylglycerol, phosphatidylethanolamine, or dioleoylphosphatidylcholine.

Lopez-Berestein et al. teach p-ethoxy antisense oligonucleotides encapsulated in a liposome comprised of neutral lipids, including liposomes composed of phosphatidycholine, phosphatidylglycerol, phosphatidylethanolamine, or preferably dioleoylphosphatidylcholine (see for example column 1, line 66 and column 2, line 56).

It would have been obvious to one skilled in the art to make a composition of an antisense oligonucleotide targeted to the translation initiation codon of bcl-2 encapsulated in a

lipid, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone and using formulations, as taught Lopez-Berestein et al.

One skilled in the art would have been motivated to modify the antisense molecules taught by Evan, Reed or Green et al. by incorporating the p-ethoxy backbone taught by Lopez-Berestein et al. for the benefit of nuclease resistance, as taught by Lopez-Berestein et al. (see column 1, lines 50-56). Further, one skilled in the art would have been motivated to use the neutral lipid formulation taught by Lopez-Berestein et al. for the antisense oligonucleotide liposome compositions taught by Evan, Reed or Green et al., modified with the p-ethoxy backbone taught by Lopez-Berestein et al. because Lopez-Berestein et al. teach that liposome formulations comprised of neutral lipids, including dioleoylphosphatidylcholine, impart improved stability and cellular uptake to antisense oligonucleotides.

Further, one would have a reasonable expectation of success given that Lopez-Berestein et al. expressly teach cellular uptake of compositions consisting of a neutral lipid and an antisense compound (see column 6, lines 60-68 and column 7, lines 40-58) and further one would have a reasonable expectation of success given that Lopez-Berestein expressly teach cellular uptake of compositions consisting of a dioleoylphosphatidylcholine liposome with an p-ethoxy antisense compound (see column 7, lines 20-66).

Therefore, the inventions as a whole would have been prima facie obvious to one skilled in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

The rejection of claims 21, 24, 25 and 36 under 35 U.S.C. 112 second paragraph, in the Office Action mailed 02/01/2001 has been withdrawn.

The rejection of claims 10-20, 25 and 39-49 under 35 U.S.C. 112, first paragraph enablement, in the Office Action mailed 02/01/2001 has been maintained.

Response to Applicant's Arguments

Applicant argues, "...the Examiner has not considered the invention as a whole in setting for the present enablement rejection." Applicant further states, "...a plethora of evidence in the response to the Office Action filed on 11/10/2000, show[ed] that the methods of the invention are enabled." Applicant further argues that the previous Office Action filed 2/01/2001 "...essentially set for a rejection based on the "utility" requirement inherent in & 112, first paragraph" and cites *In Re Brana* to support the argument that "Applicants have presented ample evidence to support the usefulness of the claimed invention."

As outlined in the previous Office Action filed 02/01/2001, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications. Taken as a whole, the scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention.

The scope of the instant claims are broadly drawn to inhibiting any disease associated with bcl-2 by administering an antisense oligonucleotide targeted to bcl-2 in a neutral liposome composition to a cell expressing bcl-2 and bax. The specification discloses examples of in vitro treatment of cells using compositions which comprise a neutral liposome and bcl-2 targeted antisense wherein the viability of one cell line is decreased. Applicant provides a declaration by inventors Tari and Lopez-Berestein (Exhibit B), which asserts that the in vitro results would correlate with in vivo results. The specification further discloses one example of nude mice injected with follicular lymphoma cells were treated with a liposomal composition comprising antisense targeted to bcl-2, wherein some treated mice exhibit a reduction in proliferation of the injected lymphoma cells. Applicant provides a declaration (Exhibit C) from Dr. Richard Ford stating that nude mice have been used in preclinical animal studies and can be predictive of results in humans.

While one skilled in the art may be able to find an antisense oligonucleotide targeted to a gene encoding bcl-2 and demonstrate decreased viability of cells treated, *in vitro*, with an antisense targeted to bcl-2, the specification as filed does not teach how to administer an antisense oligonucleotide targeted to bcl-2 and further inhibit any disease associated with bcl-2, as claimed.

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from in vitro experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in*

vitro uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

Crooke further points out the difficulties of using a nude mouse model as predictive of results in humans "[o]ur experience with human tumor zenografts has shown that it is feasible to reduce target RNA and protein levels and to induce antiproliferative effects in some of these models...Moreover, although positive results have been reproducible, the variability observed in these models has been significantly greater..." and the "...discrepancies appear to derive from a failure of these agents to distribute broadly in human tumor zenografts." Crooke et al. further states "...[a] significantly challenging consideration for antisense inhibitors of genes thought to be involved in the proliferation of malignant cells, is proof of mechanism. Simply demonstrating (or filing to demonstrate) a change in the level of a target in a proliferative cell population is inadequate information to support firm conclusions about mechanism."

In view of the unpredictability in the art of antisense-based therapy, as outlined above, and the unpredictability of applicant's nude mice animal model, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation. Further, the declarations provided cannot provide support for the broadly written claims.

Applicant states that the previous Office Action "...essentially set for a rejection based on the "utility" requirement inherent in § 112, first paragraph... [and] Applicants have presented ample evidence to support the usefulness of the claimed invention."

MPEP 2164.07 states in part: "[i]f an applicant has disclosed a specific and substantial utility for an invention and provided a credible basis for supporting that utility, that fact alone does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph." MPEP 2164.01 further states that the standard for determining enablement "...require[s] that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation."

In order to practice the claimed invention, over the full scope claimed, one of skill in the art would have to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include determination of what specific cells to target with bcl-2, how to specifically deliver antisense to a target cell *in vivo* at a concentration effective to result in inhibition of the expression of bcl-2 1, and what specific diseases and conditions would be treated by the inhibition of bcl-2. Additionally, this undue experimentation would include determination of such factors as dosage *in vivo*, disposition of the antisense molecule in tissues *in vivo* and stability of the antisense molecule *in vivo*.

Further, *In Re Brana*, as stated in the previous Office action mailed 02/01/2001, requires that the in vitro results or animal models reasonably correlate with a therapeutic utility. In the instant case, there is no evidence that the mouse model disclosed would reasonably correlate with the therapeutic results broadly claimed. Additionally as stated above, usefulness of a claimed invention does not provide a basis for concluding the claims are enabled.

Therefore, due to the broad scope of the method claimed, the state of the art of antisense and the level of unpredictability of *in vivo* therapeutic application using antisense, the level of

unpredictability of the animal model, one skilled in the art would not be able to practice the method of claims 10-20, 25 and 39-49 over the full scope claimed without undue trial and error experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

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Kimberly Chong
Examiner
Art Unit 1635

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600